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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/283,431	04/01/1999	WEN-QIANG ZHOU	475.08.423	9988

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WAYNE A KEOWN
HALE & DORR
60 STATE STREET
BOSTON, MA 02109

EXAMINER
VIVLEMORE, TRACY ANN

ART UNIT	PAPER NUMBER
1635	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/19/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/283,431	ZHOU ET AL.	
	Examiner	Art Unit	
	Tracy Vivlemore	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4-9 and 12-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4-9 and 12-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Any rejection or objection not reiterated in this Action is withdrawn.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 30, 2006 has been entered.

Priority

Applicants' claim amendments to recite oligonucleotides comprising 2'-O-substituted nucleotides linked by POPS blocks that flank a region of deoxynucleotides linked by phosphorothioates have overcome the previous denial of priority. The priority date for the claimed invention is the filing date of provisional application 60/080321, April 1, 1998.

Double Patenting

Claims 4-9 and 12-14 remain provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 4-8 of copending Application No. 10/291,058.

Applicant has previously noted that a provisional obviousness-type double patenting rejection will be withdrawn when it is the only remaining rejection. However, until this should happen it is proper that the provisional obviousness-type double patenting rejection is maintained.

Claim Rejections - 35 USC § 103

Claims 4-9 and 12-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Monia et al. (Journal of Biological Chemistry 1993) in combination with Ghosh et al. (cited on IDS of 4/24/00).

The claimed invention is directed to oligonucleotides comprising regions of 2'-O-substituted ribonucleotides linked by alternating phosphodiester and phosphorothioate bonds that flank a region of deoxyribonucleotides linked by phosphorothioates. In specific embodiments, the oligonucleotides comprise between 12 and 50 or 17 and 35 nucleotides, the phosphodiester and phosphorothioate linkages are present in ratios in the range of 1:3 to 3:1, specifically one to one, two to one, one to two, two to two or three to three, and particular 2'-O-substitutions are recited.

Monia et al. teach that inhibition of gene expression by antisense oligonucleotides has been used against a variety of viral and cellular targets, but these

oligonucleotides have been unsuited for therapeutic use due to their susceptibility to nuclease degradation and further teach modified oligonucleotides have been used to overcome these disadvantages. Monia et al. teach oligonucleotides substituted at the 2' position enhance target affinity and nuclease resistance of antisense oligonucleotides but are not substrates for RNase H. To maintain both the beneficial properties of modified oligonucleotides and substrate specificity for RNase H, researchers have turned to chimeric oligonucleotides. Monia et al. teach 17 nucleotide chimeric phosphorothioate oligonucleotides comprising regions of 2'-O-substituted ribonucleotides flanking a central region, or gap, of deoxyribonucleotides. This type of chimeric oligonucleotide provides the benefits of nuclease resistance while maintaining ability to activate RNase H cleavage of the target. The substituents examined by Monia et al. include halo and O-alkyl modification and all those tested were able to inhibit gene expression as well as or better than unsubstituted oligonucleotides. Monia et al. do not teach gapped chimeric oligonucleotides wherein phosphorothioate and phosphodiester linkages are alternated.

Ghosh et al. teach that while phosphorothioate oligonucleotides are able to overcome the nuclease sensitivity of natural oligonucleotides, they suffer from the disadvantages of reduced hybridization and increased non-sequence-specific interaction with mRNA. Ghosh et al. propose that use of phosphorothioate-phosphodiester oligonucleotide co-polymers might prove suitable for antisense applications by combining the properties of both natural and phosphorothioate oligonucleotides. Ghosh et al. analyze the properties of co-polymers with alternating

phosphorothioate and phosphodiester linkages and in table 1 teach specific oligonucleotides wherein the linkages are phosphorothioate and phosphodiester bonds alternating in the ratios recited in the claims. Ghosh et al. conclude on page 31 that phosphorothioate/phosphodiester co-polymers provide the best combination of properties for antisense applications.

It would have been obvious to one of ordinary skill in the art to make the gapped oligonucleotides comprising 2'-O-substituted ribonucleotides flanking a region of deoxynucleotides taught by Monia et al. with alternating phosphorothioate and phosphodiester linkages as taught by Ghosh et al. It would have been further obvious to make oligonucleotides wherein these alternating linkages occur only in regions of 2'-O-substituted ribonucleotides. Monia et al. provide a motivation to make an antisense oligonucleotide as a gapped compound, teaching that while 2'-O-substituted ribonucleotides overcome the susceptibility to nucleases of antisense oligonucleotides they are unable to activate RNase H and the insertion of a central deoxynucleotide portion provides oligonucleotides having both high affinity and nuclease resistance as well as RNase H activity. Ghosh et al. provide a motivation to use alternating phosphodiester/phosphorothioate linkages, teaching that use of co-polymers overcomes the disadvantages of all phosphorothioate oligonucleotides and provides the best combination of properties. Given the teachings of the art of both gapped oligonucleotides and co-polymers of alternating internucleoside linkages and the motivations to use them, the person of ordinary skill in the art would recognize that both the production of oligonucleotides having a particular pattern of internucleoside

linkages, including using alternating linkages only within regions of 2'-substitution, and the use of a particular 2'-substituent is mere design choice performed as part of routine optimization in order to make antisense oligonucleotides having the best properties for a desired application. One of skill in the art would have had a reasonable expectation of success in combining the teachings of Monia et al. and Ghosh et al. because the ability to synthesize oligonucleotides containing 2'-O-substituted sugars and both phosphorothioate phosphodiester linkages and in any pattern was routine in the art at the time of invention.

Therefore, the invention of claims 4-9 and 12-14 would have been obvious, as a whole, to one of ordinary skill in the art at the time the instant invention was made.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tracy Vivlemore whose telephone number is 571-272-2914. The examiner can normally be reached on Mon-Fri 8:45-5:15.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz, can be reached on 571-272-0763. The central FAX Number is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight

(EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For more information about the PAIR system, see http://pair-direct.uspto.gov.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Tracy Vivlemore
Examiner
Art Unit 1635
TV
January 11, 2007